

Remarks

Rejections under 35 U.S.C. §103

A. Unpredictability

On pages 3 of the Action, the Office rejects claims 1-13 and 23-29 under 35 U.S.C. §103(a) as being unpatentable over International Publ. No. WO 96/03387 to Weier et al.

The Office states that Weier et al. teaches 4, 5-substituted imidazolyl compounds and their use as anti-inflammatory agents.

The Office alleges that the compounds taught by Weier et al. are isomers of Applicant's claimed compound wherein R₁ is methyl, R₂ is halogen substituted phenyl, R₃ is C1-8 alkyl, X is C and Y is N. The Office further alleges that one of the differences between the claimed compounds and that of Weier et al. lies in that these compounds are positional isomers, i.e., the position of attachment of the halogen substituted phenyl group in the prior art is through carbon, while the present application claims a N-attachment of the substituted phenyl ring. In view of this, the Office concludes that the claimed compounds are structurally so closely related to the compounds of the reference as to be structurally obvious. The Office states that structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. The Office refers to In re Norris, 84 USPQ 458 (1950).

As agreed upon with Examiner Sadeed in a telephone conversation of June 20, 2003, Applicants have not taken into consideration the references to CAS Abst. RNs. 212630-39-2, 212630-38-1 and 212630-40-5 on the last line of page 3 of the Office Action and have read the reference to Bridges et al. on line 5 of page 4 of the Office

Action as a reference to Weier et al. A printout of the compounds associated with the subject CAS Abst. RNs. is attached for the Office's review. If Applicants understanding that these CAS numbers have been referred to in the Office Action in error is incorrect, Applicants respectfully request further explanation of the basis of any rejection based on these compounds and issuance of a further non-final Office Action to ensure a full dialog between the Office and Applicants.

The Office's argument that the present invention would be obvious in view of Weier et al. is based on the premise that a person skilled in the art would expect a positional isomer of certain compounds of Weier et al. to have properties similar to such compounds.

However, Applicants respectfully submit that the prior art strongly suggests that this is not the case. The prior art evidences that the art of diarylimidazoles is highly unpredictable. For example, the Khanna et al. reference, which notably was co-authored by Richard M. Weier, teaches in the paragraph bridging pages 1639 and 1640 that positional isomerization of a CF₃ group of the 1, 2-diarylimidazoles disclosed in this paper from position 4 to position 5 leads to loss of activity against the COX-2 enzymes up to a concentration of 100μM. The same reference also teaches under "Conclusions" on page 1641 that "[d]etailed SAR studies on the different portions of the molecule indicate that their potency, selectivity, and *in vivo* profile are greatly influenced by the substitution pattern."

Thus, Applicants respectfully submit that the Khanna et al. reference shows that the person skilled in the art would **not** have expected positional isomers of a certain diarylimidazole to have properties similar to said diarylimidazole. In fact, Khanna et al. support that the person skilled in the art of diarylimidazole would lack the motivation to make the modifications the Office suggests with any reasonable expectation of

success. The Khanna et al. reference further bears witness to the fact that a substantial degree of unpredictability exists in the art of diarylimidazole. Thus, even if the Office had established a *prima facie* case of obviousness based on a structural similarity of the compounds of Weier et al and the presently claimed compounds, which Applicants deny, the evidence of unpredictability presented would rebut any presumption of obviousness. See in particular *In re May*, 197 USPQ 601, 611 (CCPA 1978) discussing *In re Wilder*, 195 USPQ 426 (CCPA 1977) and MPEP §2144.09.

Khanna et al. was cited in the international search report and should be part of the USPTO file. However, if this is not the case, the Examiner is urged to call the undersigned, who will promptly transmit a copy of the Khanna reference to the Office.

B. Unexpected Results

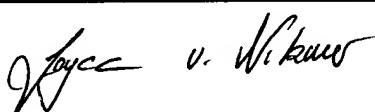
Weier et al. disclose in Table II on pages 196 and 197, the activity of 4,5 - diarylamidazoles according to their invention. A 1998 paper by Barta et al., which was written by the inventors of the Weier et al. patent publication reports the activities of selected compounds of Weier et al.

Attached hereto is a declaration by Carmen Almansa, the first named inventor of the present application as well as Table A which reflects the results of experiments conducted in the laboratory of Carmen Almansa. Table A shows the IC₅₀s of a wide array of compounds according to the presently claimed invention in human cell lines. These values, as the attached declaration explains, are directly comparable to the IC₅₀s reported in Barta et al. and are indirectly comparable to the IC₅₀s reported in Table II of Weier et al. The declaration demonstrates that the compounds according to the presently claimed invention are significantly more active than the compounds of Weier et al. For example, the declaration establishes that 1-(4-Fluorophenyl)-2-methyl-5-(4-methylsulfonylphenyl) imidazole (Example 6 of the present application), which is the

claimed compound, wherein R₁ is methyl, R₂ is 4-fluorophenyl, R₃ is CH₃, X is C and Y is N and which is one of the compounds that the Examiner alleges on page 3 of the Office Action to be obvious over Weier et al. is about 90 times more active than 5-(4-Fluorophenyl)-2-methyl-4-(4-methylsulfonylphenyl)-1H-imidazole (Example 6 of Weier et al.). For a full discussion, the Examiner is referred to the declaration and Table A.

In view of the above, Applicants respectfully submit that the rejected claims are non-obvious in view of the Weier et al. reference.

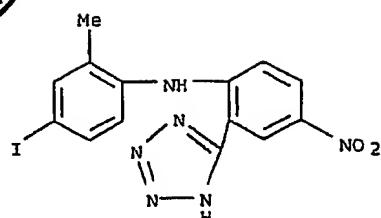
In the event that this paper is not accompanied by the full fee required for its consideration, the Commissioner is authorized to charge any insufficient or missing fees to RFEM's deposit account No. 02-2135. The Commissioner is also authorized to deposit any overpayment to the same account. A duplicate copy for the Financial Branch is enclosed.

RESPECTFULLY SUBMITTED,			
NAME AND REG. NUMBER	Joyce von Natzmer, Reg. No. 48,120		
SIGNATURE		DATE	6/30/03
Address	Rothwell, Figg, Ernst & Manbeck 1425 K Street, N.W., Suite 800		
City	Washington	State	D.C.
Country	U.S.A.	Telephone	202-783-6040

SEARCHED

Answer 1:

212630-40-5



-5 References

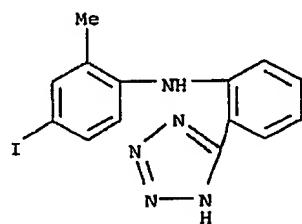
REGISTRY (Copyright 2003 ACS)

Additional Information:

3D Model

Answer 2:

212630-39-2



-9 References

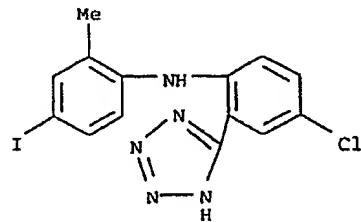
REGISTRY (Copyright 2003 ACS)

Additional Information:

3D Model

Answer 3:

212630-38-1



-9 References

REGISTRY (Copyright 2003 ACS)

Additional Information:

3D Model